Title: Prolidase Deficiency *GeneReview*- Partially successful or unsuccessful treatments

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Date: June 2015

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**Oral proline** has been tried at various doses, including 1 g/day [Arata et al 1986], 4 g/day [Isemura et al 1979], 6 g/day [Ogata et al 1981], and 10 g/day [Sheffield et al 1977], all without success.

**Topical proline.** Jemec & Moe [1996] reported significant reduction in ulcer size ($p<0.02$) after application of 5% proline ointment consisting of white Vaseline with liquid paraffin, with daily dressing changes. Dunn & Dolianitis [2008] tried topical proline 5% in white soft paraffin ointment daily and occluded beneath non-stick dressings; the ulcers reportedly improved compared to the pre-treatment period, but it did not prevent new ulcers from appearing.

Wet proline dressings applied for six months did not prove beneficial by Ogata et al [1981]. Arata et al [1986] tried a 1% proline ointment without improved results, with the strength increased to 5% and then to 10%, still with no improvement.

**Topical proline plus topical glycine.** Arata et al [1986] applied a 5% proline-5% glycine ointment thickly once daily followed by covering with a dressing gauze and bandage. They reported healing of the ulcers, with no change in imidodipeptiduria. Jemec & Moe [1996] reported significant reduction in ulcer size ($p<0.02$) after application of 5% proline plus 5% glycine ointment consisting of white Vaseline with liquid paraffin, with daily dressing changes. This mixture reportedly caused a more rapid reduction in ulcer size as compared to 5% proline alone ($p<0.02$).

However, application of 5% proline and 5% glycine ointment was also used without success by other authors [Berardesca et al 1992].

**Vitamin C.** De Rijcke et al [1989] 4 g/day of ascorbic acid with reported healing of ulcers, but the patient decided to discontinue the treatment two years later, with the ulcers reappearing soon afterwards.

However, other authors found that no ulcer improvement to vitamin C treatment [Berardesca et al 1992, Monafo et al 2000], with doses as high as 3 g/day [Arata et al 1986, Bissonnette et al 1993].

**Manganase.** Manganese chloride has been tried without success [Berardesca et al 1992]. Pedersen et al [1983] treated a patient with $MnCl_2$ in doses of 5 and 10 mg/day, followed by addition of vitamin C 2 g/day and later on also proline 2 g/day. The skin almost normalized except for slight diffuse telangiectasia and brownish pigmented spots (but with improvement of ulcers), and reportedly there was improved IQ as well.

However, other authors reported no improvement with this therapy [Monafo et al 2000]. Leoni et al [1987] administered manganese 1.18 mg/d, followed by 1.64 mg/d, plus vitamin C 1 g/day, with no improvement noticed in the ulcers.

**Dapsone.** It was administered at a dose of 75 mg/day for 2.5 months in one patient, with accelerated epithelialization of the ulcer, although with no tendency to heal earlier [Ogata et al 1981].

**Steroids.** Yasuda et al [1999] presented a patient whose ulcers did not respond to oral prednisolone <20 mg/day. Methylprednisolone IV at 1g/day for 3 days was then given, repeated three times over 2 years. This produced almost complete regression of the ulcers 1-2 months after each pulse, followed by oral prednisolone 30 mg/day. A second patient reported by the same authors showed similar results, but with a few remaining ulcers enlarging one year after stopping prednisolone.

High dose steroids caused partial regression of manifestations in other cases [Palumbo et al 2010]. Oral steroids were reported to be unsuccessful by other authors [Dunn & Dolianitis 2008].

**Skin grafting.** Ogata et al [1981] performed split-thickness skin grafting for coverage of ulcers in a patient, with temporary success reported for one month before loss of the graft. In a second individual reported by the same authors, the skin grafts were lost two years after the procedure. It was also reported as unsuccessful by other authors [Palumbo et al 2010].

**Blood transfusions.** Endo et al [1982] transfused a patient with 800 ml of whole blood, with RBC prolidase activity increased to around 35% of normal values, but gradually decreasing over time with a half-life of 41 days. The patient's ulcer was slightly improved, and there was no significant change in imidodipeptiduria. Berardesca et al [1992] performed repeated transfusions of concentrated RBCs, a total of six transfusions every two months. The ulcers of their patient decreased in size and some completely healed following the fourth transfusions, but the ulcers had recurred by follow-up 18 months after the last transfusion. They showed increased RBC prolidase activity following the transfusion, but the imidodipeptiduria remained unaltered.

However, blood transfusions were given unsuccessfully by other authors [Ogata et al 1981, Monafo et al 2000].

**Plasmapheresis**. Monthly aphreresis exchanges for four months were performed in two patients, with a reported improvement of skin ulceration [Lupi et al 2002].

**Hematopoietic stem cell transplantation.** Caselli et al [2012] performed an allogenic stem cell transplant, with successful engraftment demonstrated by full-donor chimerism. The post-transplant RBC prolidase activity had increased to carrier levels, and imidodipeptiduria was decreased. However, the patient died on day +92 from an invasive fungal infection.

Another patient undergoing hematopoietic stem cell transplant also showed increased RBC prolidase activity post-transplant, but with no clinical improvement in the frequency or appearance of the ulcers [Authors, personal observation].

**Growth hormone.** Replacement therapy with recombinant human growth hormone at 15 IU/$m^2$/week subcutaneously was associated with considerable improvement in the ulcers after two months [Monafo et al 2000]. Topical growth hormone was then combined with the systemic treatment, consisting of 4 IU of a sterile powder of growth hormone added to 50 ml of ointment containing Vaseline and cod-liver oil. After 1 month of this combined systemic-topical treatment, the ulcers had healed completely, but they recurred 6 months later despite treatment.

The authors are also aware of other cases of anecdotal healing of ulcers with topical growth hormone application [Authors, personal observation].

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